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(54) Title: PHARMACEUTICAL PRODUCT AND PREPARATION METHOD THEREOF

(54) Bezeichnung: PHARMAZEUTISCHES MITTEL UND VERFAHREN ZUR SEINER HERSTELLUNG

(57) Abstract

he products and the oral dosed forms containing an active substance are used for the treatment of patients who suffer from an abnormal distribution and a retention of liquids or products. The dosed forms are appropriate for the prophylactic treatment of patients who may generate a renal blockade. The invention may also be used for the prophylactic treatment of patients who have a tendency to form renal calculi or who form those calculi. In general, health troubles may be treated which are related with a renal missfunctioning resulting in a renal insufficiency for which appropriate measures have to be taken.

(57) Zusammenfassung

Neue Mittel und orale Dosierungsformen einer aktiven Substanz zur Behandlung von Patienten, die an einer abnormalen Verteilung und Retention von Körperflüssigkeiten oder Retentionsprodukten leiden. Die erfindungsgemässen oralen Dosierungsformen eignen sich für eine prophylaktische Behandlung von Patienten, die ein Nierenversagen entwickeln können. Die Erfindung kann ebenfalls zur prophylaktischen Behandlung von Patienten dienen, die eine Neigung zur Niersteinbildung haben, oder zur Behandlung von Patienten, die Nierensteine bilden. Allgemein können Gesundheitsstörungen behandelt werden, die im Zusammenhang mit einer gestörten Nierenfunktion und damit einer Niereninsuffizienz stehen, oder es können diesbezügliche korrigierende Massnahmen getroffen werden.

Description

PHARMACEUTICAL ORAL DOSAGE FORMS OF AN ACTIVE AGENT CAPABLE OF FORMING OR RELEASING BICARBONATE IONS

This invention relates to novel agents and oral dosage forms of an active substance for treating patients suffering from abnormal distribution and retention of body fluids or retention products.

Accompanied by corrections of body fluid distributions, such as may be achieved by increasing renal function with oral dosage forms of the invention, increased passage of retention products normally entrained in the urine can also be achieved. Furthermore, oral dosage forms of the invention are useful for prophylactic treatment of patients liable to contract renal failure. The invention also enables prophylactic treatment and treatment of patients having or being inclined to form kidney stones. In general, the common feature of the variety of ailments which can be treated or the corrective measures which can be taken are associated with altered renal function or renal insufficiency. Previous attempts which might be said to relate to the considerations of the present invention have not comprised recognition of the patient condition which should be established in order to achieve the treatment procedures indicated, and In any event no convenient means for establishing such patient condition have been available.

Physiological studies have shown that a deficit of sodium bicarbonate in the blood and extracellular fluid can lead to a condition described as acidotic volume expansion Another physiological phenoen is that the healthy kidney generates and retains more bicarbonate in the body when a deficiency of fluid in the blood and extracellular volume arises. In this fashion, a healthy patient subjected to body fluid volume contraction will enter into a state of moderate alkalosis.

The above physiological phenomena have not in the past been recognised as providing potential for therapeutic treatment of ailments and illnesses associated with altered kidney function. Thus, athough there have been suggestions in the past to attempt neutralising chronic states of metabolic acidosis, for example by intravenous injection of sodium bicarbonate solution, such procedures have in general been considered to involve some danger to the patient1 particularly when the patient is suffering from high blood pressure as is frequently the case. Similarly, the generally recognised teachings suggest that hypersodemia can develop following on such administration which can lead to such consequences as high blood pressure,cardiac insufficiency, and pulnonary and peripheral edema. Overall, there is a strong prejudice against administration of sodium bicarbonate in the treatment of ailments associated with altered renal function. hIhat is not generally knoam however is that complications such as have been experienced and described, are in fact not as a direct result of the presence of sodium bicarbonate itself, but rather of secondary changes in sodium, potassium, and calcium levels. This cold not easily be recognised in view of the lack of availability of suitable laboratory methods.

Attempt to neutralise, even in part, metabolic acidosis for example by administration of sodium bicarbonate has in general been avoided for reasons such as already mentioned and more particularly since bicarbonate loading of a patient has incorrectly been considered to depress renal function.

In contrast to practically all indications of the past, it has been found in accordance with the invention that administration of an alkaline acting substance, in particular one which liberates sodium and bicarbonate ions, in sufficient amount to raise patient plasma bicarbonate level, can in a large number of cases be highly effectively employed in the therapeutic or prophylactic treatment of a large variety of ailments involving abnormal distribution and retentIon of body fluids such as may be the result of altered renal function.

Furthermore, it has been found that acute renal failure can be prevented by prophylactic oral administration of quantities of sodium bicarbonate in a special pharmaceutical oral dosage form, for example preliminary to severe medical and surgical treatment, or ixm.ecliatlv following severe intoxications. Exemplary are kidney transplant recipients and donors, preoperative conditioning of patients with varying degrees of renal insufficiency, such as may be related to diabetes, age and pregnancy.

in connection azith establishing doses to be administered, it is most preferable to establish a so-called plasma base excess, A consideration related to this preference is the fact that observations made in reversing of acute renal failure, namely to the point where polyuria sets in, have reflected a preliminary almost simultaneous increase in fresh patient urine pH value to about neutral or alkaline suggesting passage of excess bicarbonate.

It is recognised that patients suffering from chronic renal disease characteristically display, irrespective of the type of such disease, an increase in retention products, such as hydrogen ions, sodium, urea, creatinine and uric acid, which are normally discharged through the kidneys. When these substances attain a certain level, a clinical picture of uremia is obtained, which is a threat to life and can ultimately only be treated with the aid of the artificial kidney. Due to the increased concentration of hydrogen ions, which accompanies the increase of these substances which should be eliminated by urine entrainment, hyperacidity or, metabolic acidosis results. 11pence, patients with advanced renal insufficiency characteristically display a marked hyperacidity, which has also been recognised to at least be a partial cause of various other states of ill health, such as disorders in bone metabolic and mineral metabolism.

From the experience in treating , preventing and conditioning against acute renal failure, the possibilities of advantage of neutralising at least in part metabolic acidosis as described above have in spite of countless earlier attempts been further examined. Administration of substances having an alkaline effect in an effort to neutralise metabolic acidosis have, for example, been attempted by intravenous injection of sodium bicarbonate solutions;
K.E. Thoma in "wed. Klin." 71 (1976) 124-127. Furthermore, the oral administration of a hexa potassium-hexasodium pcnta-citrate-hydrate-compl ex or a potassium-free hexacalcium hexasodium-heptacitrate-hydrate-cornpiex is described in uDiagnostih" 10 (1977) 569-572. However, intravenous injection would not be an acceptable procedure for therapy of chronic renal insufficiency and the oral administration described leaves much to be desixed in that larger amounts of these complexes need to be taken with large amounts of liquid, which frequently causes flatulence, nausea, diarrhoea and vomiting. Moreover, these complexes are in part eliminated undigested. It is accordingly difficult to or impossible to achieve sodium bicarbonate levels produced by metabolism of the complexes required for correcting metabolic acidosis.

Also generally knowh for many years is the use of sodium bicarbonate for treating acid indigestion, again a procedure creating flatulence, nausea and possibly vomitting. Such administration basically involves treatment of hyperacidity in the stomach and generally involves single irregular doses.

Attempt which might be made to employ sodium bicarbonate to neutralise at least in part metabolic acidosis can only have limited success in that relatively large amounts would be required to raise plasma sodium bicarbonate content sufficiently to exercise an adequate corrective effect on metabolic acidosis. Yt is noted here that the amounts of sodium bicarbonate required to correcting metabolic acidQsls would lead tQ deyelqpwent of substantial amounts of sodium chloride in the stomach an increased discharye of hydrochloric acid by the stomach and hence yet further development of amounts of sodium chloride.

Patients suffering from renal insufficiency are inclined to suffer from hypertension and increased amounts of sodium chloride, which has a hypertensive effect, is accordingly of stro! disadvantage particularly in that hypertension is of high danger to the patient's life expectancy.

The overall views held today in the r.edncal profession is that attempt to neutralisemetabo3icacidosis in chronic renal failure, leads to disadvantages which outweigh any advantages which may be achieved. A variety of reasons are reported, and there exists : an overall préjuaice against administration of sodium bicarbonate. One example additional to hypertension is that increased sodium in the body leads to edema.

It is an object of this invention, to establish an acceptable procedure for raising plasma bicarbonate levels without need to resort to intravenous administration (such as would be necessary in acute patient conditions) and avoiding complicatIons of the nature discussed above. Essentially, it has been found that increase of plasma bicarbonate levels is of extreme benefit in spite of the prejudice against such approach. Indeed, the finding of an acceptable procedure for increasing plasma bicarbonate levels has revealed evtraordinary utility in the most varying types of ailments, including practically any form df abnormal body fluid retention. For example, elderly patients (who might also be suffering from incomplete renal function) exhibiting such conditions as dropsy, peripheral edemas, varicose veins and like disturbances have in many cases respor.ded extraordinarily ç;ell te treatment with pharmaceutical oral dosage forms of the present invention.

Particularly, the present studies and the phannaceutical preparation which has emanated therefrom, is related to treatment of abnormal distribution and retention of body fluids which result from altered renal function.

It has been found that increase of plasma bicarbonate levels to correct at least in part metabolic acidosis existent in patients suffering frond renal insufficiency has extraordinarily and surprisingly beneficlal effects. Thus, it has been found that substantial correction of metabolic acidosis in such patients can in a large number of cases enormously increase urine production and similarly enormously increase clearance of retention - products
Effects are in some cases so marked that patients who would in due course need to be subjected to blood dialysis can either not need to be subjected to this form of treatment at all, or such can be considerably postponed. Apparently, the increase in plasma bicarbonate level and consequent correction of metabolic acidosis induces an alkalotic volume contraction of the nature discussed in the initial stages of this specification.

This driving force is believed to enable remaining functioning sections of the kidney to increase in function, i.e. urine output, sometimes to an extent sufficient for a petient, en dialysis patients to remain in an adequate metabolic state of water and acid-base balance.. Moreover, tha state of bicarbonate-induced aikalotic volume contraction nay have the effect of lowering elevated blood pressure, which is a finding of considerable surprise since all indications to date are that sodium bicarbonate administration leads to-the reverse result.

The procedure for treatment of the above nature involves increasing plasma bicarbonate levels by oral a & ninistration of oral dosage forms of the present invention t50re particularly, although other alkaline acting substances might find application in this method of the present invention, the alkaline acting substance-would be adapted to form or release bicarbonate ions. Release of bicarbonate ions and availability thereof to restore depleted extracellular reserves in metabolic acidosis is at this time considered to be a key factor.

It Is most preferable to administer sufficient -alkaline acting substance to achieve a plasma base excess in the patient, which can for example very easily be monitored by determining fresh patient urine pH value. Thus, for example, fresh patient urine p'H values in the neutral to alkaline region provides a convenient means to confirm alkalotic patient condition.

The means to establish the high alkaline level by oral administration necessary to achieve increased plasma bicarbonate level is achieved in a fashion considered to be of high importance and value in that it involves both the entirely dferent therapeutic approach described above and

also a
The alkaline acting substance is easily resorbed and very surprisingly this takes place without the variety of complicatlons such as mentioned in conjunction with administration cf alkaline acting substances employed in the past. ore particularly, the alkaline acting substance, which is one z capable of forming or releasing bicarbonate ions, is formed into a pharmaceutical oral dosage form adapted to release the alkaline acting substance in the alkaline environment of the small intestine, notably at resorption sites. Very considerably higher razzles of resorption as compared to resorption which may take place follwing on a release of the alkaline acting substance in the acid environment of the stomach can be achieved., Accordingly, correspondingly lower dosages to achieve the desired elevated plasma bicarbonate levels can be employed.

In accordance with the invention, a container comprising the pharmaceutical oral dosage form of the invention would be accompanied by indications of suitability of its contents for use In the prophylaxis or therapy of abnormal distribution or retention of body fluids or retention products in a mammalian subject. Instructions would preferably include reference to a specified amount of the contents to be swallowed by a mammalian subject for controlling said distribution or retention of body fluids or retention. The specified amount would in general be indicated to be sufficient to establish (or maintain) fresh urine pH value of the subject in the neutral to alkaline range at a pH of least 6.5 and preferably at a pH of between 6.8 and 8.

The pharmaceutical oral dosage form is, in accordance with the invention, an agent for increasing the plasma bicarbonate level of a mammalian subject and which also enables prophylactic or therapeutic effects to be achieved in the subject. The therapeutic effects which may be achieved are, more specifically, related to treatment of a subject suffering from abnormal retention of body fluids or retention products.

The pharmaceutical oral dosage forms of the invention are characterised by being substantially free of undesirable side effects known to exist for oral dosage forms of gastrointestinal bicarbonate-releasing preparations. The active agent employed in the dosage forms of the invention essentially needs to be one which forms or releases or which has been adapted in the oral dosage form to form or release bicarbonate ions only in the intestine of a subject, without the possibility of reaction thereof with gastric secretions in the stomach of the subject. Additional to the specific oral dosage forms discussed above, it is noted that further oral dosage forms can be devised and are contemplated by the present invention.

The benefits of increasing plasma (or blood) bicarbonate level in accordance with procedures of the invention may for example be achieved with an active agent capable of forming or releasing bicarbonate ions following on reaction with intestinal secretions, such as following on reaction with enzymes present in intestinal secretions.

Enzymes are in general sensitive to pH and the active agent capable of forming or releasing bicarbonate ions may be protected from reaction with gastric secretions in the stomach of the subject by being associated with enzymes which are activated only in the environment of the intestine of a subject.

It has also been found that oral dosage forms of the invention, i.e. oral dosage forms adapted to form or release resorbable bicarbonate ions only in the intestine of a subject, may comprise a carbonate, such as sodium carbonate. Thus, provided that regions of over-alkalinity which can lead to irritation or damage to the walls of the small intestine can be avoided, carbonate ion release in the small intestine of a subject leads to formaction of two bicarbonate ions via reaction with water and reaction of liberated hydroxy ions with carbon dioxide available.

A variety of methods are available to avoid regions of over-alkalinity as a result of carbonate ion release.

A procedure which.is of relative theoretical simplicity but which requires careful control and

specialised production techniques is to provide sustained slow release forms which release amounts of carbonate at a limited rate avoiding higher concentrations and enabling adequate distribution and opportunity for reaction to form bicarbonate ions.

Another procedure which is more simply realised in practice is to limit higher concentrations of carbonate ions by including smaller amounts of carbonate by dilution with a substance which releases another anion which does not generate such alkalinity. In view of requirements for availability of relatively high bicarbonate amounts in many of the uses of the oral dosage forms of the present Invention, the substance employed for releasing another anion is advantageously a bicarbonate. Thus, mixtures of a carbonate and a bicarbonate, with or without sustained release adaptions but necessarily adapted to release carbonate or bicarbonate ions in the intestine of a subject, provides a suitable source of bicarbonate ions which can be of some advantage over employment of bicarbonate alone in that amounts of carbonate and bicarbonate required to form or release a determined number of equivalents of bicarbonate ions would be lower than the amount of bicarbonate alone required to form or release the same determined number of equivalents of bicarbonate ions.

The relationship by weight of carbonate: bicarbonate in an oral dosage form of the invention comprising these two substances as bicarbonate releasing substances may be from 1 : 10 to 10 : 1 . However, in order to avoid risks of alkalinity which is higher than acceptable to the walls of the small intestine, the amount of carbonate would in general be 50 X by weight or less of the total amount of the substances for releasing bicarbonate ions comprised in the oral dosage forms of the invention.

Exemplary unit oral dosage forms of the present
invention which comprise So X by weight of sodium carbonate and So X by weight of sodium bicarbonate as sodium and bicarbonate releasing substances, comprise a total of from about 23O mg to about looo mg of alkaline acting substance in order to achieve formation or release of about the same number of equivalents of bicarbonate ions as Soo to 15oo mg of sodium bicarbonate alone. Reductions in the amount of alkaline acting substance for releasing bicarbonate ions in the small intestine can be of some benefit since, as already mentioned, relatively large amounts of alkaline acting substance need to be administered in many of the uses and therapies for which the dosage forms of the present invention are intended.

Exemplary unit oral dosage forms of the invention suit
able for treatment procedures of the invention may
comprise the following constituents:
Core compositions
1) Bicarbonate forming or releasing substance 200 to 1000 mg
;) Adjuvants 20 to 20G mg
3) Potassium supplement 0 to IOC mg
4) Magnesium supplement 0 to 500 mg
5) Calcium supplement 0 to 200 mg
6) Further active agents 0 to 200 mg
7) Trace element components 0 to 10 mg
8) Colorants, carriers 0 to 100 mg
The core composition should possess a
consistency enabling formation of a non-refractory tablet,
dragee, granulate or capsule form. The form should also pre
ferably be stable at temperatures well in excess of the temperature of warm-blooded animals, and preferably in excess of about 500 C.The formation of the dosage form should be effected in an environment of defined temperature and humidity conditions.

An exemplary coating composition suitable for coating a tablet form comprises the following essential constituents:
Cellulose acetate phthalate

Acrylic resin
An exemplary coating composition suitable for coating a capsule form to resist decomposition and reaction with gastric juices comprises the following essential constituents:
Gelatine
Hydroxymethylcbllulose phthalate
Dibutyl phthalate.

Although It may be expected that pharmaceutical oral dosage forneas discribed above may be prepared with relative' simplicity, practical experience has reflected that certain extreme care areas in the procedure need to be observed.

Particularly, one area, when employing an alkaline acting agent and a coating which is sensitive to degradation at higher pH values, is that very substantially anhydrous conditions need to be observed throughout the preparation procedure.

Another area is that the active agent needs to be uniformly and completely enclosed within a coating of pH-sensitive substance, without any points of weakness enabling premature penetration of the coating.

In accordance with the invention, there is furthermore provided a process for producing a pharmaceutical oral dosage form of an active agent capable of forming or releasing bicarbonate ions, which comprises the steps of preparing a solution of a pH-sensitive substance which is decomposable at a pH in excess of about 6, said substance being very substantially free of water and the solvent
for employedgpreparing said solution similarly being very substantially free of water, preparing a core of said active agent which is also very substantially free of water, creating an atmosphere about
of said core which has a relative humidity/lower than 40 %, applying said solution of the pH-sensitive substance to the surface of said core, and allowing said solvent to evaporate to obtain a pharmaceutical oral dosage form of the active agent which is uniformly and completely enclosed within a coating of said pH-sensitive substance.

The pH-sensitive substance may be celluloseacetate-phthalate and the solvent employed for preparing a solution of the pHsensitive substance would be of a non-alcoholic carbohydrate having from 1 to 5 carbon atoms, possessing ready volatility.

A halogenated carbohydrate such as methylene chloride is preferred The solution of the pH-sensitive substance may comprise a softening agent, pigment or protective agent.

The protective agent would preferably impart a gloss to the surface of a final pharmaceutical oral dosage form.

An additional importantfactorin preparing pharmaceutical ora7" dosage for of the invention is that the coating procedure proceed at high rate. This may be achieved by including a relatively high proportion by weight of the pH-sensitive substance in the solution, such as in excess of 5 % by weight, and preferably between 7 to 10 X by weight. Furthermore, in order to achieve said~high rate-coating,- the above mentioned readily volatile solvent is employed and the atmosphere about the core to which the solution is to be applied is maintalned at a relatively high high temperature, in excess of 350 C and preferably higher than 406 C but lower than 550 C
In order to ensure that a uniform and completely enclosed dosage form is achieved, the core is freed of all sharp corners and Irregularities at the surface to obtain a polished surface core form which is very substantially free of water.

The core of the active agent may be produced by initially forming a granulate which is very substantially free of water and pressing the granulate to obtain a core form comprising a unit dosage amount of the active agent.

The granulate, additional to comprising the actLve agent would in general comprise a granulating agent dissolved in a solvent, and optionally a binding agent, each component being very substantially free of water, and in which said granulate is freed of solvent before being pressed to obtain the core form.

The granulate may be associated with an expanding agent to encourage distribution of the active agent when this is set free in the intestine of a mammalian subject.

To ensure that no particles, particularly of active agent adhere to coatings applied in the procedure described above, the atmosphere surrounding the polished surface core form is entirely freed of all core form components before applying said solution of the pH-sensitive substance to the surface of said core.

A specific example of a core composition and unit dosage form is as follows:
Sodium bicarbonate 750.000 mg
Polyvinylpyrrolodone 22.500 mg
Binding agent (glycerides) 20.000 mg
Potato starch 10.000 mg
Silicium dioxide, colloidal 5.000 mg
Magnesium stearate 15.000 mg
822.500 mg
A specific example of a coating composition, in an amount for a unit dosage form is as follows:
Cellul oseacetatephthalate 64.000 mg
Softening agent 7.300 mg
Pigments 6.800 mg
Protecting agent (gloss) 2.800 mg
80.900 mg
Exemplary unit dosage forms found to be convenient comprise from about 200 to about 1500 mg of alkaline acting substance, such as sodium bicarbonate. Unit dosage forms may be tablets, capsules or dragees enclosed by an acid-resistant (gastric-juice resistant) alkali-decomposable enclosure.

It is appropriate to mention at this juncture, and particularly in relation to dosages tcr be administered in accordance with treatment procedures and in accordance with the present invention, that correction of metabolic acidosis insofar as such may have been attempted in the past, has lacked proper recognition of the necessary plasma bicarbonate level, the need for maintenance of such level, and at least in the case of treatment of metabolic acidosis conditions (of even slight degree) which are existent in renal insufficiency circumstances, means whereby sufficient alkaline acting substance such as a substance capable of releasing a cation such as sodium, and bicarbonate ions, has not been available.

Clinical evaluations have reflected that best results are achieved in the treatment of abnormal body fluid distribution such as result from altered renal function when the amount of alkaline acting substance administered is sufficient to create (and maintain) a moderate degree of metabolic alkalosis.

Thus, as may be determined by blood gas analysis, bicarbonate concentrations in plasma should preferably lie above 24 mEg/l and most preferably above 26 mEq/l, which corresponds to about a 4 to 5 mEq/l base excess value.

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Additional active agents, which may be included in in the oral dosage forms of the invention are aspartic acid or
derivatives thereof. Thus, it is observed that aspartic acid or
derivatives thereof comprised in asparagus,increase urine pro

duction. Anaspartate specifically contemplated and which may be included in the oral dosage forms of the invention is magnesium aspartateormagnesium aspartate hydrochloride.This ma9nesiumcompound has also been found to lower uric acid values in patients receiving gout remedies.

Dosages which need to be applied to achieve values such as descr'bed above are of course dependent on the particular condition being treated. However, in general, it has been found that dosages ranging between 0.5 and 10 g/24 hours are adeguate to establish preferred fresh patient urine pH value of above 6.5 and most preferably neutral to alkaline at a pH value between 6 8 and 8.

Indeed, most preferably, in view of indication reflected in the therapy of renal insufficiency, adequate renal function is regularly only established while fresh patient urine pH values are in the neutral to alkaline range.

It has already been indicated above that increased urine volume established by increased plasma bicarbonate levels leads to an associated increased elimination of retention products. Another surprising factor is that various conditions of edema, have been observec to be alexiated.

This is of particular note in that increased sodium levels, such as would be expected from administration of sodium bicarbonate, have in the past been considered to be a cause of edema.

There has been invention above of treatment of a variety of ailments reflected by abnormal distr bution and retention of body fluids, for example as may occur in old age, pregnancy and dietary indiscretion. The oral preparation of the present invention, it should be noted can advantageously comprise additional active agents. For example, the oral preparations of the present invention may comrpise a nutrient such as glucose, phosphates, and amino acids, a diuretic, urea, digestive acids, and enzymes. Furthermore, or purposes of of a calcium product, such as calcium qluconate or an amount of a potassium compound, such as potassium chloride, potassium bicarbonate and potassium citrate, may be included in the oral preparations of the invention.

It has been observed above that the treatment procedures of the present invention also ccmprise prophylactic approachs. One prophylactic approach worthy cf invention is prevention of the formation of kidney stones. Such prop:iy- lactic action may be encouraged by inclusion in oral preparations of substances such as alkali -or alkali earth metal citrates, or inclusion of urea itself. Thus, where increased urine volume may be encouraged by creating a state of alkalotic volume contraction, presence of increased amounts of citrate or urea in the urine volune can decrease tendencies of kidney stone formation. In lise manner, presence of increased amounts or citrate or urea in increased urine volumes can regularly be successfully emplo* to assist in the elimination of kidney stone ines and kidney stones.

For purposes of maintaining a general state or-. ell-being, particularly in elderly patients, trace elements today recognised to contribute to such may be included ill oral preparations. Already mentioned is that elderly people commonly suffer from altered renal function.

A major consideration of the present invention-is associated.

with the finaing that effective therapeutical treatment of
altered renal function can be achieved by oral administration
of an alkaline acting substance, in particular one capable normally present in extracellular fluids, and more particularly sodium bicarbonate. Some consideration has been applied to methods which might be attempted to circumvent the concepts of this invent ion, for example by associating enteral administrations of pharmaceuticals of recognised therapeutic value with sodium bicarbonate. For this reason also, it is here explicitly stated that the present invention recognises and claims hereinafter oral preparatIons, particularly such as may be employed in the therapy of a large variety of diseases and ailments which can be as a result of partial or temporariw altered renal function, which comprises alkaline acting substance such as sodium and bicarbonate ion liberating substances, in association with further pharma- ceuticalc .

Cral preparations of the present invention are highly erfective in increasing urine volume when administered at correct minimum dosage levels as described and have been found to exercise extraordinarily beneficial effects in the therapy of a multitude of body fluid distribution and fluid retention disorders.

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Claims

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Claims

1. A container accompanied by indications of suitability of its contents for use in the prophylaxis or therapy of abnormal distribution or retention of body fluids or retention products in a mammalian subject, the contents comprising a pharmaceutical oral dosage form comprising an active agent capable of forming or releasing bicarbonate ions, the active agent being one which forms or releases or which has been adapted in the oral dosage form to form or release bicarbonate ions only in the intestine of the subject without the possibility of reaction thereof with gastric secretions in the stomach of the subject.

2. A container accompanied by instructions for a mammalian subject to swallow a specified amount of its contents for controlling the distribution or retention of body fluids or retention products in said subject, the contents comprising a pharmaceutical oral dosage form comprising an active agent capable of forming or releasing bicarbonate ions, the active agent being one which forms or releases or which has been adapted in the oral dosage form to form or release bicarbonate ions only in the intestine of the subject without the possibility of reaction thereof with gastric secretions in the stomach of the subject.

3. A container according to claim 2, in which the specified amount is indicated in the instructions to be sufficient to establish fresh urine pH value of the subject in the neutral to alkaline range at a pH of at least 6.5 and preferably at a pH of between 6.8 and 8.

4. A container according to claim 3, in which the specified amount is indicated in the instructions to be sufficient to maintain said fresh urine pH value.

5. As an agent for increasing the plasma bicarbonate level of a mammalian subject and which also

enables prophylactic or therapeutic effects to be achieved in the subject, a pharmaceutical oral dosage form comprising an active agent capable of forming or releasing bicarbonate ions, the active agent being one which forms or releases or which has been adapted in the oral dosage form to form or release bicarbonate ions only in the intestine of the subject without the possibility of reaction thereof with gastric secretions in the stomach of the subject.

6. As an agent of claim 5, in which the therapeutic effects to be achieved are for treating a mammalian subject suffering from abnormal retention of body fluids or retention products. 7. A pharmaceutical oral dosage form of an active agent capable of forming or releasing bicarbonate ions, characterised in that said oral dosage form Is substantially free of undesirable side effects known to exist for oral dosage forms of gastro intestinal bicarbonate-releasing preparations, the active agent being one which forms or releases or which has been adapted in the oral dosage form to form or release bicarbonate ions only in the intestine of a subject without the possibility of reaction thereof with gastric secretions in the stomach of the subject.

8. A pharmaceutical oral dosage form according to any one of claims5, 6 or 7 , in which the active agent is one which formsor releases bicarbonate ions following on reaction thereof with intestinal secretions.

9 . A pharmaceutical oral dosage form according to claim 8, in which the active agent is one which forms or releases bicarbonate ions-following on reaction . ; * with enzymes present in intestinal secretions.

10. A pharmaceutical oral dosage fonn according to any one of claims 5, 6 or 7 , in which the active agent has been adapted in the oral dosage form to form or release bicarbonate ions only in the intestine of the subject by being associated with an additional substance enabling the active agent to form or release bicarbonate ions only following on reaction with intestinal secretions.

11. A pharmaceutical oral dosage form according to claimlo,in which said additional substance comprises enzymes which are activated only in the environment of the intestine.

12. A pharmaceutical oral dosage form according to claim lo,in which said additional substance comprises a gastric-secretion-resistant intestine secretion-decomposable material.

13. A pharmaceutical oral dosage form according to claim I?,in which the active agent has been coated with said additional substance.

14. A pharmaceutical oral dosage form according to claim 13tin which the gastric-juice-resistant small-intestine-decomposable enclosure comprises a gastric-juice resistant acrylic resin.

15 A pharmaceutical oral dosage form according to claim 13,in which the gastric-juice-resistant small-intestine-decomposable enclosure is a capsule enclosure rendered resistant to gastric juice with the aid of a mixture of gelatine hydroxypropyl methyl cellulose phthalate and do butyl phthalate.

16. A pharmaceutical oral dosage form according to claim 13,in which the gastric-juice-resistant small-intestine-decomposable enclosure is a tablet coating rendered resistant to gastric juice with the aid of cellulose acetate phthalate.

17. A pharmaceutical oral dosage form according to any one of claims 5, 6 or 7, in which the active agent is selected from the group consisting of a bicarbonate, a carbonate, or a mixture of a bicarbonate and a carbonate at a ratio by weight of from 1 : 10 to 10 : 1.

18. A pharmaceutical oral dosage form according to any one of claims 5 to 17, in which the active agent is associated with a further active agent suitable for the prophylaxis and therapy of kidney stones, selected from the group consisting of an alkali metal or alkaline earth metal salt of citric acid, and urea.

19. A pharmaceutical oral dosage form according to any one of claims 5 to 17, in which the active agent is associated with a calcium compound suitable for supplementing calcium in the subject.

20. A pharmaceutical oral dosage form according to claim 19, in which the calcium compound is calcium gluconate.

21. A pharmaceutical oral dosage form according to any one of claims 5 to 17, in which the active agent is associated with a potassium compount suitable for supplementing potassium in the subject 22. A pharmaceutical oral dosage form according to claim 21, in which the potassium compound is selected from the group consisting of potassium chloride, potassium bicarbonate, and potassium citrate.

23. A pharmaceutical oral dosage form according to any one of claims 5 to 22, in which trace elements recognised to contribute to the general well-being of subjects are comprised in the oral dosage form.

24. A pharmaceutical oral dosage form according to claim 17, in unit dosage form, comprising from about 200 to about 1500 mg of a bicarbonate

enclosed within a gastric-juice-resistant small-intestine-decomposable enclosure enabling release of bicarbonate ions only in the intestine of the subject.

25. A process for producing a pharmaceutical oral form of an active agent capable of forming or releasing bicarbonate ions, which comprises the steps of preparing a solution of a pH-sensitive substance which isdecomposable at a pH in excess of about 6, said substance being very substantially free of water and the solvent employed for preparing said solution similarly being very substantially free of water, preparing a core of said active agent which is also very substantially free of water, creating an atmosphere about said core which has a relative humidity lower than 40 %, applying said solution of the pH-sensitive substance to the surface of said core, and allowing said solvent to evaporate to obtain a pharmaceutical oral dosage form of the active agent which is uniformly and completely enclosed within a coating of said pH-sensitive substance.

26. A process according to claim 25, in which the pH sensitive substance is celluloseacetate-phthalate.

27. A process according to claim 25 or 26, in which the solvent employed for preparing the solution of the pH-sensitive substance is a non-alcoholic carbohydrate having from 1 to 5 carbon atoms.

28. A process according to claim 27, in which the solvent is a halogenated carbohydrate.

29. A process according to claim 28, in which the solvent is methylene chloride.

30. A process according to any one of claims 25 to 29, in which any one or more of a softening agent, pigment and protective agent are additionally comprised in the solution of the pH-sensitive substance.

31. A process according to any one of claims 25 to 30, in which the amount of pH-sensitive substance comprised in the solution is in excess of 5 t by weight.

32. A process according to claim 31, in which the amount of pH-sensitive substance comprised in the solution is between about 7 and lo % by weight.

33. A process according to any one of claims 25 to 32, in which the coating of pH-sensitive substance is effected with relative rapidity by including a relatively high proportion by weight of the pH-sensitive substance in the solution, by employing readily volatile solvent and by maintaining the atmosphere about the core

to which the solution is to be applied at a relatively high temperature, in excess of 350 C and preferably higher than 40 C but lower than 550 C.

34. A process according to any one of claims 25 to 33, in which the core of the active agent is produced by initially forming a granulate which is very substantially free of water, pressing the granulate to obtain a core form comprising a unit dosage amount of the active agent, and freeing the core of all sharp corners and irregularities at the surface to obtain a polished surface core form which is very substantially free of water.

35. A process according to claim 34, in which said granulate comprises the active agent, a granulating agent dissolved in a solvent, and optionally a binding agent, each component being very substantially free of water, and in which said granulate is freed of solvent before being pressed to obtain the core form.

36. A process according to claim 34 or claim 35, in which said granulate is associated with an expanding agent to encourage distribution of the active agent when this is set free in the intestine of a mammalian subject.

37. A process according to any one of claims 34 to 36, in which the atmosphere surrounding the polished surface core form is entirely freed of all core form components before applying said solution of the pH-sensitive substance to the surface of said core.

38. A process according to any one of claims 25 to 36, in which the active agent capable of forming or releasing bicarbonate ions is selected from a bicarbonate, a carbonate, or a mixture of a bicarbonate and a carbonate at a ratio by weight of from 1 : lo to lo : 1 39. A process according to claim 38, in which the active agent at least comprises sodium bicarbonate.

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